VOLUME 33 · NUMBER 14 · MAY 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter Phase II Trial of Temsirolimus and Bevacizumab in Pancreatic Neuroendocrine Tumors

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Published online ahead of print at www.jco.org on December 8, 2014.

Supported by National Cancer Institute Contracts No. N01 62205, N01 62203, N01 62208, N01 62209, N01 62206, N01 62204, N01 62207, N01 62201, HHSN261201100070C, and N01-CM-00080.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT01010126.

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0732-183X/15/3314w-1551w/$20.00

DOI: 10.1200/JCO.2014.56.2082

ABSTRACT

Purpose

There are few effective therapies for pancreatic neuroendocrine tumors (PNETs). Recent placebo-controlled phase III trials of the mammalian target of rapamycin (mTOR) inhibitor everolimus and the vascular endothelial growth factor (VEGF)/platelet-derived growth factor receptor inhibitor sunitinib have noted improved progression-free survival (PFS). Preclinical studies have suggested enhanced antitumor effects with combined mTOR and VEGF pathway–targeted therapy. We conducted a clinical trial to evaluate combination therapy against these targets in PNETs.

Patients and Methods

We conducted a two-stage single-arm phase II trial of the mTOR inhibitor temsirolimus 25 mg intravenously (IV) once per week and the VEGF-A monoclonal antibody bevacizumab 10 mg/kg IV once every 2 weeks in patients with well or moderately differentiated PNETs and progressive disease by RECIST within 7 months of study entry. Coprimary end points were tumor response rate and 6-month PFS.

Results

A total of 58 patients were enrolled, and 56 patients were eligible for response assessment. Confirmed response rate (RR) was 41% (23 of 56 patients). PFS at 6 months was 79% (44 of 56). Median PFS was 13.2 months (95% CI, 11.2 to 16.6). Median overall survival was 34 months (95% CI, 27.1 to not reached). For evaluable patients, the most common grade 3 to 4 adverse events attributed to therapy were hypertension (21%), fatigue (16%), lymphopenia (14%), and hyperglycemia (14%).

Conclusion

The combination of temsirolimus and bevacizumab had substantial activity and reasonable tolerability in a multicenter phase II trial, with RR of 41%, well in excess of single targeted agents in patients with progressive PNETs. Six-month PFS was a notable 79% in a population of patients with disease progression by RECIST criteria within 7 months of study entry. On the basis of this trial, continued evaluation of combination mTOR and VEGF pathway inhibitors is warranted.

J Clin Oncol 33:1551-1556. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are uncommon tumors of the endocrine cells of the pancreas, with a generally indolent but relentlessly progressive behavior.[1] Effective systemic therapies for patients with PNETs are lacking. The only randomized trial in PNETs to demonstrate an overall survival (OS) benefit was a small study published more than two decades ago, with the combination of streptozocin and doxorubicin established as a standard therapy.[2] More recently, temozolomide-based regimens have been commonly employed based on phase II[3] and retrospective data.[4] Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), and sunitinib, a tyrosine kinase inhibitor of several receptors related to angiogenesis, have both demonstrated improvement in progression-free survival (PFS) compared with placebo for patients with PNETs.[5,6] Randomized trials of everolimus and sunitinib enrolled patients deemed to have experienced disease progression in the previous 12 months, although by no defined criteria. These two trials resulted in remarkably similar results for both placebo (median PFS, 4.6 and 5.5

months) and experimental arms (median PFS, 11.0 months with everolimus and 11.4 months with sunitinib). Objective responses were rare (< 10%).

Interfering with multiple pathways that affect tumor cells and the tumor microvasculature is a promising strategy in PNETs. Temsirolimus, an mTOR inhibitor, targets essential regulatory functions in the tumor as well as the tumor microenvironment, including the production of vascular endothelial growth factor (VEGF) through HIF1α. Bevacizumab, by neutralizing VEGF-A, targets the tumor endothelium. Preclinical studies have suggested that the combination of the mTOR inhibitor rapamycin with a monoclonal antibody against VEGF is associated with enhanced antitumor effects in a pancreatic cancer model, compared with each agent alone.[7] The combination also was associated with a more potent in vivo antiangiogenic effect, as measured by tumor microvessel density, and enhanced apoptosis. This led to a phase I/II trial of bevacizumab combined with temsirolimus in advanced renal cell carcinoma performed by the Mayo Clinic Phase II Consortium, which demonstrated the tolerability of the combination at the full single-agent dose of each drug.[8]

On the basis of our phase I data on these agents, the single-agent activity of both mTOR and VEGF pathway inhibition in PNETs, and the suggestion of the benefit of this combination, we set out to evaluate the combination of temsirolimus and bevacizumab in a multiinstitution phase II trial for patients with a clinical need for active therapy. Previous trials[9,10] by our group and others used progressive disease within 6 months as an entry criterion. To maximize accrual in a trial for a rare tumor, we chose for pragmatic reasons to enroll patients with progressive disease by RECIST criteria (version 1.1)[11] within 7 months of enrollment, given the roughly 3- to 6-month intervals of clinical follow-up common at participating institutions.

PATIENTS AND METHODS

Patients

Eligible patients had histologically confirmed locally advanced or metastatic, well or moderately differentiated NETs with clear evidence of pancreatic origin, were age ≥ 18 years, and had an Eastern Cooperative Oncology Group performance status of 0 to 1. Evidence of progressive disease as documented by RECIST (version 1.1) within 7 months before study entry was required. This was to approximate the eligibility criterion of progressive disease within 6 months used in prior trials by this group and others but to allow 7 months to maximize accrual in patients with a rare disease and frequently used follow-up intervals of roughly 3 to 6 months. Adequate organ function, urinalysis with < 2+ protein, fasting serum cholesterol ≤ 350 mg/dL, and triglycerides ≤ 1.5× upper limit of normal were required. Patients who had received prior anthracycline chemotherapy were required to have normal left ventricular ejection fraction before registration. Submission of archived tumor, blood, and serum for translational studies was required.

Prior systemic treatments for metastatic disease were permitted, including ≤ two prior cytotoxic chemotherapy regimens, interferon, radiolabeled somatostatin analog therapy, and/or other investigational therapy. Prior octreotide and/or continued octreotide at a stable dose was allowed, but not mandated, if a patient had experienced progression at that dose. Prior hepatic arterial therapies for liver metastases were permitted. All prior treatment had to be completed ≥ 4 weeks before registration. No prior therapy with mTOR or VEGF pathway inhibitors was allowed. Patients with significant cardiovascular disease, untreated CNS metastases, surgical resection of CNS metastases within 3 months of registration, or a major surgical procedure or evidence of bleeding event within 6 months of registration were excluded from the study. Patients with known HIV infection or who were pregnant or breastfeeding were excluded.

The institutional review boards of each participating medical center and the National Cancer Institute approved the protocol. Written informed consent was obtained before patients entered the study.

Study Design and Treatments

This study was a multicenter, single-arm, open-label phase II trial. The coprimary end points were objective tumor response rate (RR) and 6-month PFS. Patients were treated with temsirolimus 25 mg intravenously (IV) on days 1, 8, 15, and 22 and bevacizumab 10 mg/kg IV on days 1 and 15 of a 28-day cycle. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal. Dose interruption or discontinuation of bevacizumab was permitted for adverse events. Temsirolimus dose modifications to 20, 15, or 10 mg were allowed, and once reduced, the dose could not be re-escalated with subsequent treatments. If either bevacizumab or temsirolimus was omitted or discontinued, the patient could continue to receive the other agent during the study.

Study Assessments

Clinical and laboratory evaluations were performed every 4 weeks. Adverse events were assessed using the Common Terminology Criteria for Adverse Events (version 3.0). Chromogranin A (if elevated at baseline) and any clinically relevant hormone produced by the patient's tumor were tested every 8 weeks. Radiographic evaluation using RECIST (version 1.1) by triple-phase computed tomography or magnetic resonance imaging scan was performed every 8 weeks by the local investigator.

Statistical Considerations

The coprimary end points of this study were confirmed objective RR and 6-month PFS. A confirmed tumor response was defined as either a complete or partial response (PR) noted as the objective status on two consecutive evaluations at least 8 weeks apart. All patients meeting the eligibility criteria who signed a consent form and received at least one dose of study treatment were evaluable for response. Patients who died without documentation of progression were considered to have experienced disease progression on the date of their death. If patients received at least one dose of study treatment and had not experienced disease progression at 6 months, they were considered progression free at 6 months.

The study was conducted using a modified two-stage Simon's design with a fixed sample size of 50 patients. Up to 55 patients were to be accrued to account for 10% dropout. If more than two of the first 25 evaluable patients enrolled achieved a confirmed tumor response during the first six cycles of treatment, or more than 15 of the first 25 evaluable patients enrolled were progression free at 6 months, enrollment would continue to the second stage of another 25 evaluable patients. If neither end point was reached, patient accrual was to be terminated, and the regimen would be considered inactive in this patient population. This was derived by assuming an alternative hypothesis of 20% (v historical control rate of 5%) for RR and an alternative hypothesis of 80% (v historical control rate of 60%) for 6-month PFS.

Descriptive statistics such as mean (± standard deviation), median (range), and frequency (percentage) and statistical graphs were used to summarize patient characteristics, toxicity, and tumor response. Kaplan-Meier methodology was used to summarize PFS and OS.

RESULTS

Patients

A total of 58 patients were enrolled between September 2009 and May 2012. The actual dropout rate was higher than expected (ie, eight [16%] of 50); hence, more than the planned 55 patients were enrolled. Excluding two patients who withdrew consent before initiating therapy and six ineligible patients, we reached exactly 50 evaluable patients

Table 1. Patient Clinical and Demographic Characteristics (N = 58)

Characteristic	No.	%
Age, years		
Median	58.5	
Range	29.0-81.0	
Sex		
Female	29	50.0
Male	29	50.0
ECOG performance status		
0	29	50.0
1	29	50.0
Ethnicity		
White	49	85.0
African American	8	13.0
Hispanic or Latino	1	2.0
Months from diagnosis to enrollment		
Median	13.7	
Range	0.3-176.3	
Prior therapy		
None	23	
Octreotide	29	
One prior chemotherapy regimen	13	
Two prior chemotherapy regimens	5	
Chemoembolization	4	
PRRT	2	
Follow-up time, months		
Median	24.5	
Range	2.3-49.1	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PRRT, peptide receptor radionuclide therapy.

per protocol. These six ineligible patients were ineligible solely because of a lack of sufficient tissue submission for the translational study; they received protocol therapy and were therefore, after careful deliberation, included in the safety and efficacy analyses. Baseline demographics and clinical characteristics are listed in Table 1. Median age was 58.5 years; 50% of patients were female; 50% had an Eastern Cooperative Oncology Group performance status of 1; 29 patients had received prior and/or concurrent octreotide, 13 patients had received one prior chemotherapy regimen, and five of these had received two prior regimens; 23 patients had received no prior systemic therapy. Median follow-up for all patients was 24.5 months (range, 2.3 to 49.1 months).

Safety

Adverse events are listed in Table 2. The most common grade 3 to 4 adverse events (noted by ≥ 5% of patients) were hypertension (21%), fatigue (16%), lymphopenia (14%), hyperglycemia (14%), thrombocytopenia (12%), headache (7%), mucositis (7%), neutropenia (7%), anemia (7%), and proteinuria (7%). Median duration of temsirolimus treatment was 6.5 cycles; for bevacizumab, it was nine cycles. Median duration of any therapy (either agent or both) was 9.5 cycles. Dose reductions of temsirolimus for toxicity occurred in 82% (46 of 56) of patients. Dose interruptions of bevacizumab occurred in 25% (14 of 56) of patients. Seventeen patients (30%) discontinued study treatment because of adverse events or refusal. Although the specific reason or reasons for discontinuation because of adverse events was not collected, a review of last-cycle toxicity revealed grade 2 to 3 fatigue and/or mucositis in more than half of these patients.

Table 2. Adverse Events Occurring in ≥ 10% of Patients (n = 56)*

Event	Grade 1 to 2 (%)	Grade 3 to 4 (%)
Hypertension	32	21
Fatigue	63	16
Hyperglycemia	29	14
Lymphopenia	20	14
Thombocytopenia	54	12
Mucositis	52	7
Proteinuria	50	7
Headache	30	7
Neutropenia	30	7
Anemia	58	7
Abnormal liver function test	51	5
Hypokalemia	11	5
Hypercholesterolemia	59	5
Bleeding	38	5
Infection	28	4
Diarrhea	27	4
Skin rash	41	2
Anorexia	43	0
Edema	20	0
Renal failure	11	0

*Includes all patients who initiated therapy.

Efficacy

For the 56 patients eligible for efficacy analysis, objective RR was 41%. There were no complete responses. Six-month PFS was 79%. Median PFS was13.2 months (95% CI, 11.2 to 16.6; Fig 1). PFS at 1 year was 43% (95% CI, 41% to 68%). Median OS was 34.0 months (95% CI, 27.1 to not reached; Fig 2). Forty-three patients experienced progression, 31 while receiving therapy. Twenty-eight patients died, and five remained on the protocol therapy as of the study analysis. A waterfall plot of best patient response shows some tumor regression in the majority of patients (Fig 3).

Nineteen patients had an elevated level of chromogranin A (> 2 × upper limit of normal) at baseline; 14 of these patients experienced at least a 50% decrease during treatment. Among these 14 patients, nine had a confirmed PR, and 13 of them were progression

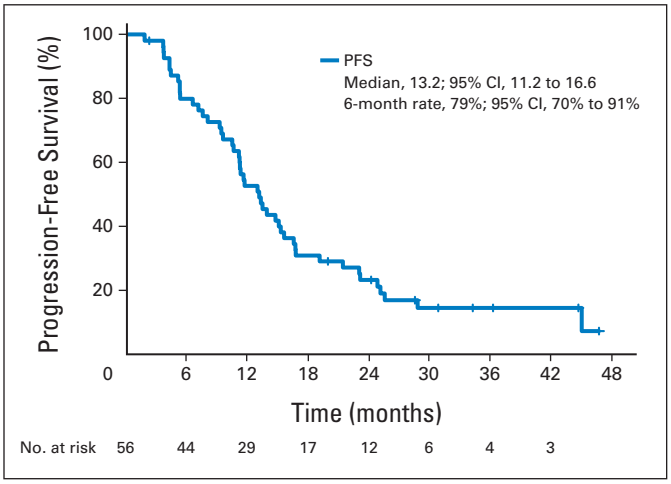

Fig 1. Progression-free survival (PFS).

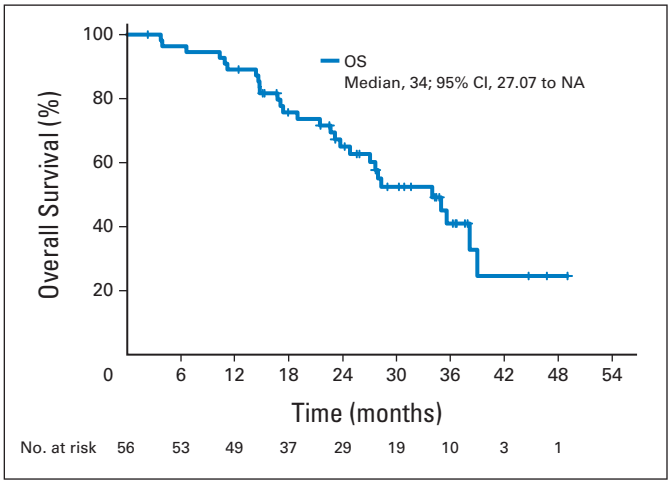

Fig 2. Overall survival (OS).

free at 6 months. Eleven patients had a clinical syndrome with hormone production measured at baseline. Five of these patients had at least a 50% decrease (three in gastrin, one in insulin, and one in serotonin). Among these five patients, two had a PR, and three were progression free at 6 months.

DISCUSSION

The activity of temsirolimus and bevacizumab in this phase II trial met or exceeded our criteria for defining a promising regimen in the treatment of progressive metastatic PNETs. The objective RR of 41% exceeded our goal of 20% and far exceeds the single-agent RRs noted for single-agent mTOR or VEGF pathway inhibitors in prior studies of patients with PNETs and progressive disease,[5,6] and the PFS at 6 months of 79% nearly met our goal of 80% for this coprimary end point.

The median PFS of 13.2 months is numerically similar to the median PFS in the phase III trials of everolimus and sunitinib (11.0 and 11.4 months, respectively), but there are significant differences in trial population and study design, which may suggest this result is promising. Patients with PNETs are a heterogeneous group with a disease that can be clinically indolent or more rapidly progressive. Our study enrolled patients who had experienced progression by RECIST criteria in a period of 7 months before enrolling onto the trial, as opposed to over 12 months by undefined criteria in the phase III trials of everolimus and sunitinib. Patients in the phase III trials were also candidates for placebo. Likely, our trial population had more clearly and rapidly progressing disease. In addition, the radiographic assessments in this study were performed every 8 weeks, as opposed to every 12 weeks in the phase III trials, likely biasing PFS results in favor of the phase III trials. As an example of potential variation in trial outcomes that may be related to the characteristics of patients enrolled, we previously conducted a trial of gefitinib of similar design in PNETs, with less stringent criteria of RECIST progression over 60 weeks required to enroll and with tumor evaluation every 8 weeks. Median PFS in the gefitinib trial was only 3.7 months, even less than that in the placebo arms of the phase III trials, despite noted clinical efficacy in some patients.[9]

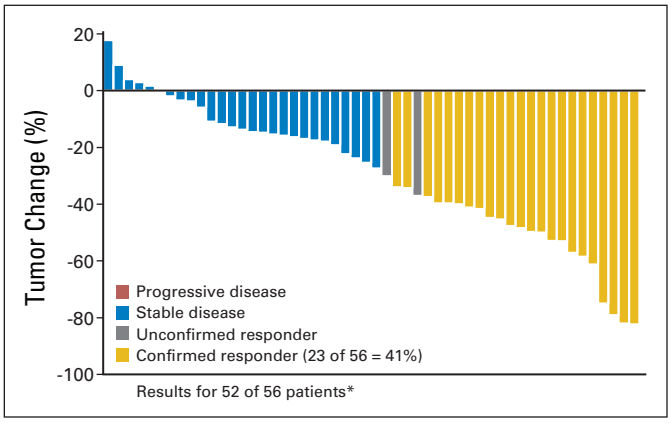

Fig 3. Waterfall plot of best response. (*) Excludes four evaluable patients who had no postbaseline measurements.

A potential limiting factor for this regimen in terms of prolonged disease control is the fact that 30% of patients discontinued therapy for reasons other than disease progression. The median PFS of 13.2 months was longer than the median duration of therapy of approximately 9 months, with a median of 6 months for the combination together. It is not clear that targeted therapies need to be delivered indefinitely to maximize impact on OS in PNETs, but this will limit PFS for a number of patients. There were many potential reasons that individual patients chose to discontinue therapy before progression, but cumulative fatigue and mucositis seemed to be significant issues for many of these patients. Although toxicity was manageable and consistent with the single-agent toxicities associated with each agent, there was a need for frequent dose reductions of temsirolimus (80% of patients), and median duration of administration was 2.5 months less than for bevacizumab.

Only 11 patients were reported to have functioning tumors with elevated circulating hormone levels. For five patients, a 50% reduction of these levels was noted, likely suggesting a potential for improvement in symptoms of hormonal syndromes with this regimen.

Bevacizumab as a single agent showed modest activity in a small trial in small intestinal carcinoid tumors,[12] and it is being evaluated in a phase III trial versus interferon in that disease. There are no data regarding the activity of bevacizumab in PNETs. It is possible that there is significant activity of this agent, which may have influenced the results of this study, rather than the putative synergy between the therapies. Single-agent temsirolimus in a population of patients with PNETs similar to the population in our study had minimal activity, with a response rate of only 7%.[10] We have opened an additional 25-patient cohort in our trial to investigate the single-agent activity of bevacizumab in this population with metastatic PNETs. Patient accrual is ongoing.

The Alliance for Clinical Trials, along with the North American GI Intergroup, is conducting a randomized phase II trial of everolimus versus the combination of everolimus and bevacizumab, with a primary end point of PFS. Accrual has been completed, and we await the results to further inform the value of this combination of targeted agents. It is noted that despite initial enthusiasm for this combination in patients with renal cell carcinoma, a randomized phase III trial showed that the combination of temsirolimus and bevacizumab was not superior to the standard combination of interferon and bevacizumab.[13]

There are limitations our trial. It was not randomized. All evaluations of response were from local investigators. In addition, no central pathology review was performed. Tumor Ki-67 was not uniformly reported, because eligibility for this trial used local pathology reports, and most reports did not document this marker, given the variable standards of the prior decade. However, patients were predominantly accrued at high-volume academic centers with excellence in radiology, pathology, and clinical trial execution.

In conclusion, the combination of temsirolimus and bevacizumab showed substantial activity in a group of patients with progressive well or moderately differentiated metastatic PNETs. The confirmed RR of 41% and the reported reduction in circulating hormone levels suggest that targeted therapies can potentially improve symptoms of tumor bulk or hormone secretion, which usually are indications for chemotherapy in this disease. The toxicity profile was consistent with the single-agent toxicities of the two agents. We await future clinical trial results of combined mTOR and VEGF therapies in PNETs, as well as results of our single-agent bevacizumab trial in PNETs, but it seems this biologic combination may become an important addition to systemic therapy for PNETs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Diane Reidy-Lagunes, Novartis (C), Pfizer (C); Manisha Shah, Novartis (U); Hedy Lee Kindler, Genentech (U); Heinz-Josef Lenz, Genentech (C), Roche (C) **Stock Ownership:** None **Honoraria:** Diane Reidy-Lagunes, Novartis; Jonathan Strosberg, Genentech, Pfizer; Heinz-Josef Lenz, Genentech, Roche **Research Funding:** Diane Reidy-Lagunes, Novartis; Jonathan Strosberg, Pfizer; Manisha Shah, Novartis; Hedy Lee Kindler, Genentech, Pfizer; Heinz-Josef Lenz, Genentech, Pfizer, Roche **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

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Final approval of manuscript: All authors

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GLOSSARY TERMS

angiogenesis: the process involved in the generation of new blood vessels. Although this is a normal process that naturally occurs and is controlled by so-called on and off switches, blocking tumor angiogenesis (antiangiogenesis) disrupts the blood supply to tumors, thereby preventing tumor growth.

bevacizumab: also called Avastin (Genentech, South San Francisco, CA). Bevacizumab is a recombinant, humanized, monoclonal antibody that binds and neutralizes the vascular endothelial growth factor, thus acting as an antiangiogenic agent.

mTORC1: complex composed of mammalian target of rapamycin (mTOR), regulatory associated protein of mTOR (raptor), and mLST8/GL. This complex has the classic features of mTOR by functioning as a sensor for nutrients and energy and controlling protein synthesis. The complex is downstream from AKT and phosphorylates S6K1 upon activation.

pancreatic neuroendocrine tumor (PNET/islet cell tumor): a relatively rare form of pancreatic cancer, in which tumors arise from the pancreatic islets of Langerhans, being composed of transformed islet cells that produce (or once produced) insulin or other polypeptide hormones. The endocrine hormone–secreting islet cells (and islet tumors) express a number of neuronal genes, reflecting an evolutionary heritage with neuronal cells, and hence their designation as neuroendocrine, to contrast them with the prevalent form of human pancreatic cancer (ductal adenocarcinoma).

targeted therapeutics: therapeutic agents that are specifically modeled to inhibit very specific molecules in signal transduction pathways implicated in the disease.

temsirolimus: an inhibitor of the mammalian target of rapamycin, a member of the phophoinositide kinase-related family proteins. Also called CCI-779.

